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Gray Zone Lymphoma: Better Treated Like Hodgkin Lymphoma or Mediastinal Large B-Cell Lymphoma?

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Abstract

Although primary mediastinal large B-cell lymphoma (PMBL) and classic Hodgkin lymphoma of the nodular sclerosis type (CHL-NS) are distinct diseases, they share several clinical characteristics and biologic features. Given that, it is not surprising that there exist mediastinal lymphomas that do not fit well into either category but have clinical and morphologic features overlapping and transitional between PMBL and CHL-NS. The term *mediastinal gray zone lymphoma* (MGZL) has been used for these tumors, which are included in the World Health Organization classification as “B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma.” Although several studies have evaluated different therapeutic strategies in PMBL and CHL-NS, there is a paucity of prospective experience treating MGZL, given its rarity and relatively recent recognition. Historically, diseases that today would be categorized as MGZL were probably called “anaplastic

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large-cell lymphoma Hodgkin-like,” and their outcome with standard approaches was poor, with short overall survivals. In this review—following a discussion of the biology and clinical features of MGZL, and how they compare to PMBL and CHL-NS—we outline how the treatment of PMBL and CHL-NS has evolved in recent years, and how we believe MGZL should be approached therapeutically.

Keywords

Hematologic malignancy; Lymphomas; Hodgkin lymphoma; Hodgkin’s disease; Classic Hodgkin lymphoma of the nodular sclerosis type; CHL-NS; Mediastinal lymphoma; Primary mediastinal large B-cell lymphoma; PMBL; Mediastinal gray zone lymphoma; MGZL; Gray zone lymphoma; GZL; Thymic B cell; Diffuse large B-cell lymphoma; DLBCL; Epigenetics; Gene expression profiling; Radiation therapy; Chemotherapy; Immunophenotyping; Microenvironment

Introduction

Although most lymphoma cases can be diagnosed and classified as one of the currently recognized distinct disease entities, some lymphomas exhibit overlapping histologic, biologic, and clinical features between various types of lymphoma. One of the important accomplishments of the most recent World Health Organization (WHO) Classification of Tumors of Haematopoietic and Lymphoid Tissues was the recognition of these entities. In the 2008 classification, the category “B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma” was introduced for the first time and lymphomas in this category are known more commonly as “gray zone lymphomas” (GZLs) [1, 2•, 3] (Table 1).

GZL refers to diseases that lie at the histologic and biologic interface between various lymphomas, and the term has been used in the context of many lymphoma subtypes [4]. In addition, synchronous and metachronous lymphomas of discordant histologies can occur and involve a combination of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Throughout this review, the term *mediastinal gray zone lymphoma* (MGZL) refers to those lymphomas where there exists morphologic, biologic, and clinical overlap between classic Hodgkin lymphoma (CHL), nodular sclerosis subtype, and primary mediastinal B-cell lymphoma (PMBL), a subtype of diffuse large B-cell lymphoma (DLBCL) (Fig. 1).

Recent progress has been made in understanding the origin of the Hodgkin/Reed Sternberg (HRS) cell, and oncologists now recognize that it is almost always a B cell. In that regard, it is not unexpected that significant biologic and clinical overlap exist between CHL and B-cell NHL [5]. HRS cells are characterized by suppression of many components of the B-cell program, and they are incapable of immunoglobulin secretion [6]. The biologic events that lead to this state are complex and poorly elucidated, and may occur in patients with normal immunity—as is the case in most patients with CHL—or in the setting of immunodeficiency [7–10].

Clinical Presentation

Although the clinical presentation of these entities is similar, there are some differences observed. PMBL has a propensity to affect females and is typically diagnosed in the third and fourth decades of life, as compared to other variants of DLBCL, which peak in incidence in the seventh decade. It most likely arises from a thymic B cell and typically presents with an anterior mediastinal mass. Symptoms at diagnosis are related to the mediastinal mass, and patients with very large masses can present with superior vena cava syndrome. Mediastinal masses greater than 10 cm are common at diagnosis, and local infiltration into adjacent structures such as the lungs and chest wall is frequently observed. The disease tends to be confined to the mediastinum at diagnosis, but at progression, or relapse it is not uncommon to have involvement of extranodal sites such as the kidneys, liver, adrenal glands, and central nervous system. It is interesting that the clinical characteristics of CHL of the nodular sclerosis subtype (CHL-NS) are very similar to PMBL—with a female preponderance, young age at diagnosis, and mediastinal presentation. CHL-NS is also likely to be of thymic B-cell origin and shares many molecular features with PMBL. Although MGZL is relatively rare, the limited published data revealed that MGZLs predominantly affect males and have a clinical presentation very similar to that of PMBL [11, 12]. Their morphologic and biologic features and clinical outcome are discussed in the subsequent sections.

Morphologic and Immunophenotypic Features

Although CHL-NS and PMBL are clinically and morphologically similar, they can be distinguished from one other on the basis of pathologic features. CHL-NS typically has a nodular growth pattern with broad fibrotic bands and lacunar variants of HRS cells. The neoplastic cells are positive for CD15 and CD30, and negative for CD45. B-cell antigen expression is typically weak; that is, CD20 is weakly or variably expressed and PAX5 and CD79a are weak or negative [13, 14]. There is lack of expression of surface immunoglobulin by the neoplastic cells, and transcription factors such as OCT2 and BOB1 are often negative [15, 16].

PMBL has characteristic histologic appearances and was first described over 30 years ago following a review of 184 NHL cases, in which 17 with aggressive histology had a mediastinal presentation [17]. The pathologist typically sees an infiltrate of large cells with round or lobulated nuclei and abundant clear cytoplasm. Features such as fine compartmentalizing sclerosis can be seen in the background, and, occasionally, cells with an HRS-like appearance can be found. Necrosis may also be present [18]. CD20 and pan-B-cell markers such as CD79a are typically positive, but surface immunoglobulin expression is absent, as in CHL [19, 20]. Although PAX5, BOB1, and OCT2 are strongly expressed, CD30 expression is variable [18, 20, 21]. CD10 and BCL6 may be positive and CD23 expression is typically seen, indicating derivation from a thymic B cell [22, 23].

The morphologic appearances of MGZL are intermediate between those of CHL and PMBL. The tumor cells are often pleomorphic, and can sheet-out and grow in a diffusely fibrotic stroma. Cells can have the appearances of PMBL or CHL, and a wide spectrum of cytologic

appearance can be observed in different areas. The background can resemble PMBL with clusters of cells similar to lacunar cells or even HRS cells. Scattered eosinophils, lymphocytes, and histiocytes may be present in a sparse inflammatory infiltrate. Immunophenotypic features of MGZL are also intermediate and transitional between the two parent entities [11, 12]. Although CD45, CD20, CD79a, and CD30 are frequently positive, CD15 may or may not be expressed. PAX5, OCT-2, and BOB1 are usually positive. MGZL can present with a Hodgkin-like morphology and a phenotypic pattern of PMBL (CD20++, CD15–). Alternatively the lymphoma can present with a PMBL-like morphology and a Hodgkin phenotype, with expression of CD30 and CD15 and loss of CD20 and CD79a [3].

A related phenomenon, but technically not considered a form of MGZL, is composite lymphoma, with some areas resembling CHL and other areas showing sheets of large B cells characteristic of PMBL. The inflammatory background and pattern of sclerosis usually corresponds to the appearance of the neoplastic cells, resembling either CHL or PMBL, respectively [1, 11].

Biologic Characteristics

Gene expression profiling studies have interestingly demonstrated that there is extensive biologic overlap between PMBL and CHL, and that the molecular profile of PMBL is much closer to that of CHL than to other subtypes of DLBCL [24, 25]. PMBL and CHL, in fact, share approximately one third of their genes [24]. PMBL shows frequent gains of gene regions on chromosome 9p (up to 75 %) and 2p (approximately 50 %). These have also been described in CHL but rarely in other subtypes of DLBCL [26]. The 9p region encodes JAK2, a tyrosine kinase that phosphorylates/ activates the transcription factor STAT6 [24, 27]. SOCS1 suppresses JAK signaling and is regularly deleted in both PMBL and CHL [28]. Other genes that may be involved at 9p are PDL1 and PDL2; c-Rel may be involved at 2p [24, 26]. A recent study of chromosomal aberrations for 2p16.1, 9p24.1, and 8q24 in children with PMBL found that the frequencies of investigated loci were similar to those found in adults [29]. Both PMBL and CHL also have constitutively activated nuclear factor κ B (NF- κ B), and genomic CIITA breaks have recently been found to be highly recurrent in both diseases [24, 30].

Interphase fluorescence in situ hybridization (FISH) studies in adults with GZL demonstrated gains including amplifications in 2p16.1 (REL/BCL11A locus), alterations affecting the JAK2/PDL2 locus in 9p24.1, rearrangement of the CIITA locus at 16p13.13, as well as gains of 8q24 at MYC [31]. At this time, the molecular signature of MGZL has not been elucidated, but a recent large-scale methylation analysis of PMBL, CHL, and MGZL demonstrated a close epigenetic relationship between these entities and a unique epigenetic signature for MGZL, validating its inclusion in the WHO classification as a separate disease [32••]. Importantly, MGZL could be distinguished from CHL-NS and PMBL by differential methylation of selected CpG islands, and a class prediction model could be established to segregate the various entities. Thus, the epigenetic signature of these lymphoma entities may be useful not only to establish new diagnostic tools and clarify the pathogenesis of these lymphomas, but also to identify possible targets for future therapies. Although material is

limited because of the rarity of MGZL, further studies are needed to explore this entity in more detail. Gene expression profiling and further genetic studies might be of great value for a more comprehensive understanding of disease pathogenesis and for establishing new and more effective therapies than currently exist [31].

Primary Management

Before discussing treatment approaches to MGZL, it is instructive to review how we approach CHL-NS and PMBL. Although standardized approaches to the treatment of CHL involving the mediastinum exist, which we discuss in the following sections, the optimal therapeutic approach and regimen choice for PMBL (and MGZL) are controversial. As these diseases are very curable and typically affect young females, the long-term effects of therapy are an important consideration, especially with respect to the administration of mediastinal radiation, which is a frequently used treatment modality in these diseases. Several sobering reports detail high incidences of, particularly, breast cancer and ischemic heart disease, several years after patients with mediastinal lymphomas received radiation therapy [33, 34•, 35, 36]. Therefore, novel strategies that maintain high cure rates but obviate the need for mediastinal radiation are needed.

Classic Hodgkin Lymphoma of the Nodular Sclerosis Type

Most reported clinical trials of CHL-NS have not specifically evaluated the outcomes of patients presenting with mediastinal disease. One study did investigate the outcome of 80 patients with HL who presented with bulky mediastinal disease. The patients received six cycles of MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)/ ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) followed by mantle-field radiation therapy; the reported disease-free survival was 76 % in those with stage I or II disease at 15 years' follow-up [37]. Another study, again in patients with massive mediastinal disease, evaluated MOPP alone. In this group, there was a very high relapse rate compared to studies where radiation was used, suggesting that combined-modality therapy is necessary [38]. Recent studies in nonbulky disease have compared ABVD alone to ABVD with radiation. In one study, 152 untreated, unselected patients with clinical stage 1A, 1B, IIA, IIB, and IIIA nonbulky disease were prospectively evaluated. They were randomized to either six cycles of ABVD alone or six cycles of ABVD followed by radiation [39]. Complete response rates, freedom from progression, and overall survival were similar in both groups at 60 months' follow-up.

Another interesting study prospectively compared the outcome of patients who received ABVD alone versus subtotal nodal radiation, with or without ABVD [40, 41••]. The results of this study were recently published, and the 12-year follow-up period allowed the authors to appreciate the longterm effects of radiation treatment that contributed significantly to overall survival. At 12 years' follow-up, the overall survival was 94 % in those receiving ABVD alone, as compared to 87 % in those receiving subtotal nodal radiation. Interestingly, in the latter group, there was a higher rate of deaths from other causes than in the ABVD group. Though both studies did not specifically enroll patients with mediastinal

presentations and included other sites of disease, the results suggest that patients with nonbulky disease do well with chemotherapy alone.

At this point, although combined-modality therapy for early stage bulky mediastinal disease is typically administered, optimal therapy of nonbulky mediastinal disease is controversial. Although the relapse rate may be lower in patients receiving mediastinal radiation, this is offset by the serious long-term consequences of radiation treatment and the high salvageability of patients who relapse after primary therapy [34•]. Unlike older studies, many current studies incorporate FDG-PET imaging for response assessment and are investigating its role in identifying patients who may do well with chemotherapy alone [42]. Many studies are also evaluating dose-intense approaches and whether they may obviate the need for combined-modality therapy [43].

Primary Mediastinal B-Cell Lymphoma

Early studies suggested that PMBL had a poor outcome with CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone) chemotherapy alone, and several studies evaluated dose-intensified regimens in this patient population. One such study of 50 untreated patients with PMBL demonstrated high efficacy of MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) followed by consolidation radiation treatment; however, 66 % of patients had a persistently positive gallium scan at the end of chemotherapy, suggesting active disease [44]. Following consolidation radiation therapy, however, only 19 % had a positive gallium scan, and 80 % were event free at 39 months' median follow-up time [44]. Later, MACOP-B and VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) were compared to CHOP in a retrospective analysis, and the outcome with the latter regimen was inferior, suggesting that dose intensity is important in this disease [45]. In another retrospective analysis, the International Extranodal Lymphoma Study Group (IELSG) compared outcomes of 426 patients with PMBL across 20 institutions where patients received MACOP-B, VACOP-B, ProMACE-CytaBOM, or CHOP, and they found an inferior outcome in the CHOP group [46]. However, there have been no prospective comparisons of these regimens. At the time when the Southwest Oncology Group (SWOG) compared CHOP to second- and third-generation regimens in DLBCL, PMBL was not recognized as a distinct entity and the outcome of patients with first- versus second- and third-generation regimens was not assessed [47]. A retrospective study that looked at the outcome of 141 consecutive PMBL patients who were treated with CHOP-like therapy or approaches that included high-dose chemotherapy suggested that dose-dense chemotherapy was superior to CHOP in these patients [48].

Although the addition of rituximab to CHOP (R-CHOP) chemotherapy in DLBCL has been shown to improve survival in several different studies, this has not been well studied in PMBL because of the disease's rarity [49]. In a retrospective study carried out in British Columbia in the pre- and post-rituximab period, there was no survival advantage in patients when rituximab was added to CHOP (the number of patients in the R-CHOP arm was small, however, and the follow-up time relatively short) [50]. A recent sub-group analysis of the prospective, randomized, phase III Mabthera International Trial (MINT) evaluated the role of

rituximab in combination with CHOP-like regimens in patients with PMBL [51]. Patients who received rituximab had an improved 3-year event-free survival (78 % vs 52 % in the chemotherapy arm alone). However, overall survival was not significantly different between the two groups. It is important to note that preplanned radiotherapy was administered to the majority of patients in both groups, and the addition of radiation improved remission rates. This study suggested that adding rituximab to CHOP may be beneficial in PMBL, but it did not demonstrate that this regimen could obviate the need for radiation. Recently, a retrospective analysis of R-CHOP (with consolidation mediastinal radiation in the majority) in 58 patients with PMBL demonstrated a high rate of initial treatment failure and a progression-free survival of 68 % at 5 years [52].

Since dose intensity appears to be important in this disease, we investigated the DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) regimen in PMBL based on its efficacy in DLBCL [53–55]. This is a pharmacodynamically dose-adjusted regimen, and this strategy may especially benefit younger patients who likely require higher doses of drugs to achieve serum drug levels similar to older patients [55]. We set out to investigate if the regimen could obviate the need for mediastinal radiation treatment and, thus, eliminate the risk of long-term consequences, such as secondary cancers and ischemic heart disease. In a recent update of 40 patients with untreated PMBL who received the regimen without consolidation radiation, the event-free survival and overall survival were 95 % and 100 %, respectively, with only two patients requiring radiation treatment at a median follow-up time of 4 years [56]. In terms of assessing the additive benefit of rituximab with this regimen, when these results were compared to a historical PMBL group who received DA-EPOCH alone (no radiation), the addition of rituximab significantly improved event-free survival (95 % vs 65 %; $p=0.0012$) and overall survival (100 % vs 77 %; $p=0.013$) [56].

How Should Mediastinal Gray Zone Lymphoma Be Managed?

This brings us to the question of how MGZL cases should be managed and whether they should be approached in the same way as CHL-NS or PMBL. As these diseases are rare, and only recently have been recognized and included in the WHO classification, just one prospective study has reported their outcome [56]. In the past, these diseases were included under the category “anaplastic large-cell lymphoma Hodgkin-like,” and this entity was associated with poor survival following standard therapy. One study evaluated the outcome of these patients following a CHL or NHL regimen, and survivals were significantly inferior to those of other HLs [57]. Recently, the survival of 16 patients with CD20-positive MGZL treated prospectively with the DA-EPOCH-R regimen was reported. Although they had similar clinical characteristics to a group of PMBL patients who received the same regimen, their event-free (45 %) and overall survival (75 %) rates were significantly inferior at 4 years’ follow-up, with a high percentage requiring mediastinal radiation [56]. The biologic basis for the adverse prognosis (compared with PMBL) of MGZL is not well understood, but studies are investigating their biology and may identify novel targets that could lead to the investigation of more effective therapies. CD20-negative MGZL is uncommonly encountered. Although CD20 may be negative, we recommend immunochemotherapy with a regimen such as DA-EPOCH-R, as there may be sensitivity issues related to the

immunohistochemical staining for CD20 and the B-cell program is likely to be important in MGZL, as it is in PMBL and CHL-NS.

Conclusions

CHLNS and PMBL are closely related diseases that share clinical and biologic characteristics, and are likely to be of thymic B-cell origin. Mediastinal lymphomas that have morphologic and immunophenotypic features intermediate between CHL-NS and PMBL but do not fit into either category are termed *mediastinal gray zone lymphomas*. Although little is known about their biology, the recent large-scale methylation study demonstrated that they have a unique epigenetic signature [32••]. Further, gene expression profiling studies comparing MGZL to PMBL and CHL-NS are awaited.

Patients with these diseases also have distinctly different outcomes. A recent study evaluated the DA-EPOCH-R regimen in patients with PMBL and reported excellent event-free survival, with very few patients requiring mediastinal radiation [56]. The treatment approach for patients with bulky mediastinal CHL-NS should include radiation treatment in the absence of evidence that it can be avoided; however, this should be investigated in future studies. For patients with nonbulky CHL-NS, recent studies suggest that chemotherapy alone may be effective and that radiation avoidance may be associated with better long-term outcomes. The optimal therapy for MGZL has not been defined, but regimens like DA-EPOCH-R are a reasonable approach. Although a proportion of MGZL patients can be cured with immunochemotherapy alone, these patients are more likely to require radiation than patients with PMBL. Future directions in these diseases should include the continuation of strategies that obviate the need for radiation and the exploration of selective targeting of pathways such as janus kinases.

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References

1. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues Lyon: IARC; 2008.
- 2••. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011;117(19):5019–5032. [PubMed: 21300984] The review discusses new concepts introduced in the 2008 WHO classification, including the concept of MGZL.
3. Grant C, Dunleavy K, Eberle FC, Pittaluga S, Wilson WH, Jaffe ES. Primary mediastinal large B-cell lymphoma, classic Hodgkin lymphoma presenting in the mediastinum, and mediastinal gray zone lymphoma: what is the oncologist to do? *Curr Hematol Malig Rep* 2011;6(3):157–63. [PubMed: 21590365]
4. Rudiger T, Jaffe ES, Delsol G, et al. Workshop report on Hodgkin's disease and related diseases ('grey zone' lymphoma). *Ann Oncol* 1998;9 Suppl 5:S31–38.
5. Jaffe ES, Zarate-Osorno A, Medeiros LJ. The interrelationship of Hodgkin's disease and non-Hodgkin's lymphomas—lessons learned from composite and sequential malignancies. *Semin Diagn Pathol* 1992;9(4):297–303. [PubMed: 1480852]
6. Kuppers R The biology of Hodgkin's lymphoma. *Nat Rev Cancer* 2009;9(1):15–27. [PubMed: 19078975]

7. Kanzler H, Kuppers R, Hansmann ML, Rajewsky K. Hodgkin and Reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. *J Exp Med* 1996;184(4):1495–505. [PubMed: 8879220]
8. Stein H, Marafioti T, Foss HD, et al. Down-regulation of BOB.1/ OBF.1 and Oct2 in classical Hodgkin disease but not in lymphocyte predominant Hodgkin disease correlates with immunoglobulin transcription. *Blood* 2001;97(2):496–501. [PubMed: 11154228]
9. Bellas C, Santon A, Manzanal A, et al. Pathological, immunological, and molecular features of Hodgkin's disease associated with HIV infection. Comparison with ordinary Hodgkin's disease. *Am J Surg Pathol* 1996;20(12):1520–4. [PubMed: 8944046]
10. Levine AM. Hodgkin's disease in the setting of human immunodeficiency virus infection. *J Natl Cancer Inst Monogr* 1998;23:37–42.
11. Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. *Am J Surg Pathol* 2005;29(11):1411–21. [PubMed: 16224207]
12. Garcia JF, Mollejo M, Fraga M, et al. Large B-cell lymphoma with Hodgkin's features. *Histopathology* 2005;47(1):101–10. [PubMed: 15982329]
13. Schmid C, Pan L, Diss T, Isaacson PG. Expression of B-cell antigens by Hodgkin's and Reed-Sternberg cells. *Am J Pathol* 1991;139(4):701–7. [PubMed: 1656757]
14. Zukerberg LR, Collins AB, Ferry JA, Harris NL. Coexpression of CD15 and CD20 by Reed-Sternberg cells in Hodgkin's disease. *Am J Pathol* 1991;139(3):475–83. [PubMed: 1716042]
15. Lodenkemper C, Anagnostopoulos I, Hummel M, et al. Differential Emu enhancer activity and expression of BOB.1/OBF.1, Oct2, PU.1, and immunoglobulin in reactive B-cell populations, B-cell non-Hodgkin lymphomas, and Hodgkin lymphomas. *J Pathol* 2004;202(1):60–9. [PubMed: 14694522]
16. Foss HD, Reusch R, Demel G, et al. Frequent expression of the B-cell-specific activator protein in Reed-Sternberg cells of classical Hodgkin's disease provides further evidence for its B-cell origin. *Blood* 1999;94(9):3108–13. [PubMed: 10556196]
17. Lichtenstein AK, Levine A, Taylor CR, et al. Primary mediastinal lymphoma in adults. *Am J Med* 1980;68(4):509–14. [PubMed: 6892753]
18. Pileri SA, Zinzani PL, Gaidano G, et al. Pathobiology of primary mediastinal B-cell lymphoma. *Leuk Lymphoma* 2003;44 Suppl 3: S21–26. [PubMed: 15202521]
19. Moller P, Moldenhauer G, Momburg F, et al. Mediastinal lymphoma of clear cell type is a tumor corresponding to terminal steps of B cell differentiation. *Blood* 1987;69(4):1087–95. [PubMed: 3103712]
20. Pileri SA, Gaidano G, Zinzani PL, et al. Primary mediastinal B-cell lymphoma: high frequency of BCL-6 mutations and consistent expression of the transcription factors OCT-2, BOB.1, and PU.1 in the absence of immunoglobulins. *Am J Pathol* 2003;162 (1):243–53. [PubMed: 12507907]
21. Higgins JP, Warnke RA. CD30 expression is common in mediastinal large B-cell lymphoma. *Am J Clin Pathol* 1999;112(2):241–7. [PubMed: 10439805]
22. Calaminici M, Piper K, Lee AM, Norton AJ. CD23 expression in mediastinal large B-cell lymphomas. *Histopathology* 2004;45 (6):619–24. [PubMed: 15569053]
23. Salama ME, Rajan Mariappan M, Inamdar K, Tripp SR, Perkins SL. The value of CD23 expression as an additional marker in distinguishing mediastinal (thymic) large B-cell lymphoma from Hodgkin lymphoma. *Int J Surg Pathol* 2010;18(2):121–8. [PubMed: 19223373]
24. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *J Exp Med* 2003;198(6):851–62. [PubMed: 12975453]
25. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin's lymphoma. *Blood* 2003;2003:2003–2006-1841.
26. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood* 2010;116(17):3268–77. [PubMed: 20628145]

27. Guiter C, Dusanter-Fourt I, Copie-Bergman C, et al. Constitutive STAT6 activation in primary mediastinal large B-cell lymphoma. *Blood* 2004;104(2):543–9. [PubMed: 15044251]
28. Melzner I, Bucur AJ, Bruderlein S, et al. Biallelic mutation of SOCS-1 impairs JAK2 degradation and sustains phospho-JAK2 action in the MedB-1 mediastinal lymphoma line. *Blood* 2005;105(6):2535–42. [PubMed: 15572583]
29. Oschlies I, Burkhardt B, Salaverria I, et al. Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. *Haematologica* 2011;96(2):262–8. [PubMed: 20971819]
30. Steidl C, Shah SP, Woolcock BW, et al. MHC class II transactivator CIITA is a recurrent gene fusion partner in lymphoid cancers. *Nature* 2011;471(7338):377–81. [PubMed: 21368758]
31. Eberle FC, Salaverria I, Steidl C, et al. Gray zone lymphoma: chromosomal aberrations with immunophenotypic and clinical correlations. *Mod Pathol* 2011;24(12):1586–97. [PubMed: 21822207]
- 32•. Eberle FC, Rodriguez-Canales J, Wei L, et al. Methylation profiling of mediastinal gray zone lymphoma reveals a distinctive signature with elements shared by classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma. *Haematologica* 2011;96(4):558–566. [PubMed: 21454882] This is the first biologic study of GZLs. It provides insight into the plasticity of immunophenotype and morphology of these tumors, and their transitional appearance.
33. Bassal M, Mertens AC, Taylor L, et al. Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2006;24(3):476–83. [PubMed: 16421424]
- 34•. Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood* 2011;117(6):1806–1816. [PubMed: 21037086] This study highlights the long-term complications of therapy, particularly radiation treatment in survivors of HL.
35. Dunleavy K, Bollard CM. Sobering realities of surviving Hodgkin lymphoma. *Blood* 2011;117(6):1772–3. [PubMed: 21310929]
36. Tukenova M, Guibout C, Oberlin O, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol* 2010;28(8):1308–15. [PubMed: 20142603]
37. Longo DL, Glatstein E, Duffey PL, et al. Alternating MOPP and ABVD chemotherapy plus mantle-field radiation therapy in patients with massive mediastinal Hodgkin's disease. *J Clin Oncol* 1997;15(11):3338–46. [PubMed: 9363863]
38. Longo DL, Russo A, Duffey PL, et al. Treatment of advanced-stage massive mediastinal Hodgkin's disease: the case for combined modality treatment. *J Clin Oncol* 1991;9(2):227–35. [PubMed: 1988570]
39. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood* 2004;104(12):3483–9. [PubMed: 15315964]
40. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *J Clin Oncol* 2005;23(21):4634–42. [PubMed: 15837968]
- 41•. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med* 2012;366(5):399–408. [PubMed: 22149921] This recent study suggests that ABVD alone versus radiation-based therapy is associated with a better long-term outcome in limited-stage HL.
42. Dunleavy K, Mikhaeel G, Sehn LH, Hicks RJ, Wilson WH. The value of positron emission tomography in prognosis and response assessment in non-Hodgkin lymphoma. *Leuk Lymphoma* 2010;51 Suppl 1:28–33. [PubMed: 20658958]
43. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 2003;348(24):2386–95. [PubMed: 12802024]

44. Zinzani PL, Martelli M, Magagnoli M, et al. Treatment and clinical management of primary mediastinal large B-cell lymphoma with sclerosis: MACOP-B regimen and mediastinal radiotherapy monitored by (67)Gallium scan in 50 patients. *Blood* 1999;94 (10):3289–93. [PubMed: 10552937]
45. Todeschini G, Secchi S, Morra E, et al. Primary mediastinal large B-cell lymphoma (PMLBCL): long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B/VACOP-B. *Br J Cancer* 2004;90(2):372–6. [PubMed: 14735179]
46. Zinzani PL, Martelli M, Bertini M, et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. *Haematologica* 2002;87(12):1258–64. [PubMed: 12495899]
47. Fisher RI, Gaynor ER, Dahlborg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993;328 (14):1002–6. [PubMed: 7680764]
48. Hamlin PA, Portlock CS, Straus DJ, et al. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factor analysis in 141 consecutive patients treated at Memorial Sloan Kettering from 1980 to 1999. *Br J Haematol* 2005;130(5):691–9. [PubMed: 16115124]
49. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346(4):235–42. [PubMed: 11807147]
50. Savage KJ, Al-Rajhi N, Voss N, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol* 2006;17(1):123–30. [PubMed: 16236753]
51. Rieger M, Osterborg A, Pettengell R, et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study. *Ann Oncol* 2011;22(3):664–70. [PubMed: 20724576]
52. Abramson J, Hellmann M, Feng Y, et al. High rate of initial treatment failure in patients with primary mediastinal B-cell lymphoma treated with R-CHOP. *Blood ASH Annual Meeting Abstracts* 2011 118:1601.
53. Wilson WH, Bryant G, Bates S, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. *J Clin Oncol* 1993;11(8):1573–82. [PubMed: 7687667]
54. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol* 2008;26(16):2717–24. [PubMed: 18378569]
55. Wilson WH PP, Hurd D, et al. Phase II study of dose-adjusted EPOCH-R in untreated de novo CD20+ diffuse large B-cell lymphoma (DLBCL)-CALGB 50103. *Proc Am Soc Clin Oncol* 2005;24.
56. Dunleavy K, Pittaluga S, Shovlin M, et al. Untreated primary mediastinal B-cell (PMBL) and mediastinal grey zone (MGZL) lymphomas: comparison of biological features and clinical outcome following DA-EPOCH-R without radiation. *Ann Oncol* 2011;22(4) Abstract 149.
57. Cazals-Hatem D, Andre M, Mounier N, et al. Pathologic and clinical features of 77 Hodgkin's lymphoma patients treated in a lymphoma protocol (LNH87): a GELA study. *Am J Surg Pathol* 2001;25(3):297–306. [PubMed: 11224599]

Fig. 1.

Interrelationships among mediastinal lymphomas. Primary mediastinal large B-cell lymphoma (PMBL), classic Hodgkin lymphoma of the nodular sclerosis subtype (CHL-NS), and mediastinal gray zone lymphoma (MGZL) are all thought to be derived from a thymic B cell. In a given patient, differing histologic patterns can be seen at different times, suggesting plasticity in tumor cell phenotype and gene expression. Composite lymphomas of CHL-NS and PMBL may also be seen. *Adapted from Grant et al. [3]*

Table 1

Clinical and biologic features of mediastinal lymphomas

	CHL-NS	PMBL	MGZL
Age at onset	Young adult	Young adult	Young adult
Sex distribution	F>M	F>M	M>F
SVC syndrome	Rare	May be present	May be present
Peripheral lymphadenopathy	May be present	Rare	Rare
CD20 staining	Weak or variable	Positive	Usually positive
2p16.1; 9p24.1	Gains, amplification	Gains, amplification	Gains, amplification
NF- κ B pathway	Activated	Activated	Activated

CHL-NS classic Hodgkin lymphoma of the nodular sclerosis subtype; MGZL mediastinal gray zone lymphoma; NF- κ B nuclear factor κ B; PMBL primary mediastinal large B-cell lymphoma; SVC superior vena cava

Adapted from Grant et al. [3]